ICU nephrology: the implications of cardiovascular alterations in the acutely ill

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Cardiovascular alterations are common in critically ill patients and can have important implications for multiple organ systems, including the kidney. Restoring and maintaining adequate hemodynamic status in such patients is crucial to ensure sufficient oxygen availability to tissues and organs so that they can function optimally. In this text, we will return to the basic physiology of cardiac output and its components so that we can better understand the effects of cardiovascular alterations in critically ill patients, and how best to treat them.

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Many, if not all, disease processes encountered in intensive care unit patients can impact directly or indirectly on hemodynamics and cardiovascular status, including obvious etiologies, such as myocardial infarction and cardiogenic shock, and less apparent facets, such as the myocardial depression of sepsis. Restoring and maintaining an adequate and appropriate hemodynamic status in such patients is crucial to ensure sufficient oxygen availability to tissues and organs, including the kidneys, so that they can function optimally. Oxygen delivery (DO_2) is determined by cardiac output and arterial oxygen content, which is itself determined by hemoglobin concentration and hemoglobin oxygen saturation (Figure 1).

Cardiovascular problems are much more complex than just a low or high arterial pressure or a low or high cardiac output. In this text, we will return to the basic physiology of cardiac output and its components so that we can better understand the implications of cardiovascular alterations in critically ill patients, and how best to treat them.

UNDERSTANDING CARDIAC OUTPUT

Cardiac output has four determinants—heart rate, contractility, preload, and afterload. To understand the individual and combined impact of these four components, we have suggested a simple analogy that equates the cardiac output, i.e., the amount of blood pumped by the heart over a period of time, to the speed of a bicycle[1] (Figure 2).

The simplest determinant of cardiac output to visualize is the heart rate, reflected by the speed of pedaling in our analogy. There is an optimal speed at which a cyclist pedals—both too slow and too fast are bad, but within a certain range changing the pedaling speed will not influence the speed of the bicycle very much. Similarly, altering heart rate is only likely to benefit when the heart rate is very low or very high. Increasing heart rate may impair left ventricular filling, and hence reduce stroke volume, and can be deleterious because heart rate is a fundamental determinant of the myocardial oxygen demand (myocardial oxygen consumption is proportional to the rate pressure product). Similarly, great care should be taken when sinus tachycardia is observed, as it usually represents either an adaptation to decreased stroke volume or a means to achieve a supranormal cardiac output. In either case, decreasing heart rate in isolation, without treating the cause of the tachycardia, would result in a

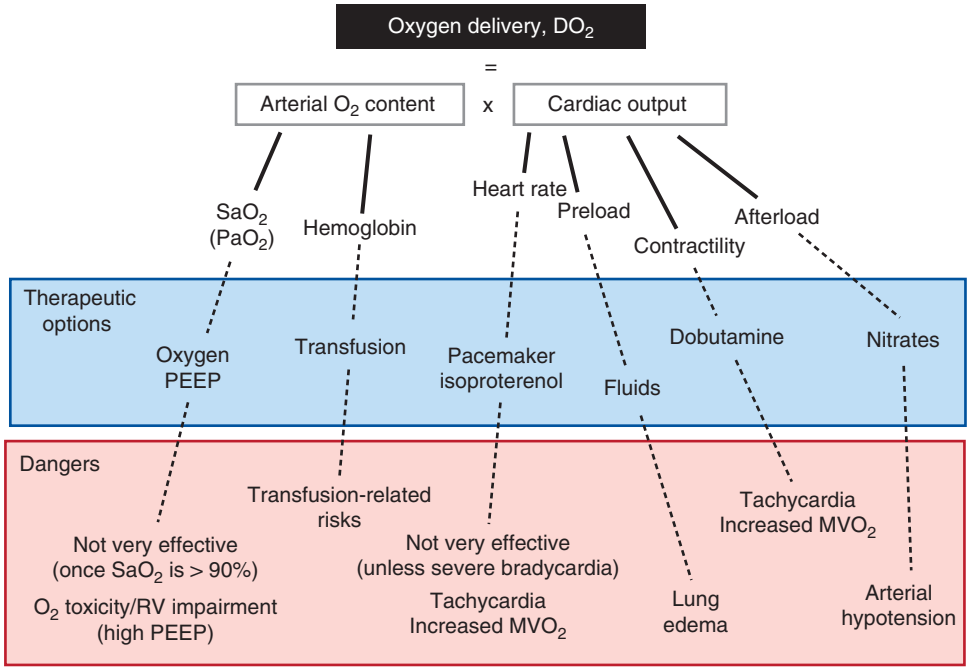

Figure 1 | The determinants of oxygen delivery. MVO_2, myocardial oxygen consumption; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; RV, right ventricular; SaO_2, arterial oxygen saturation.

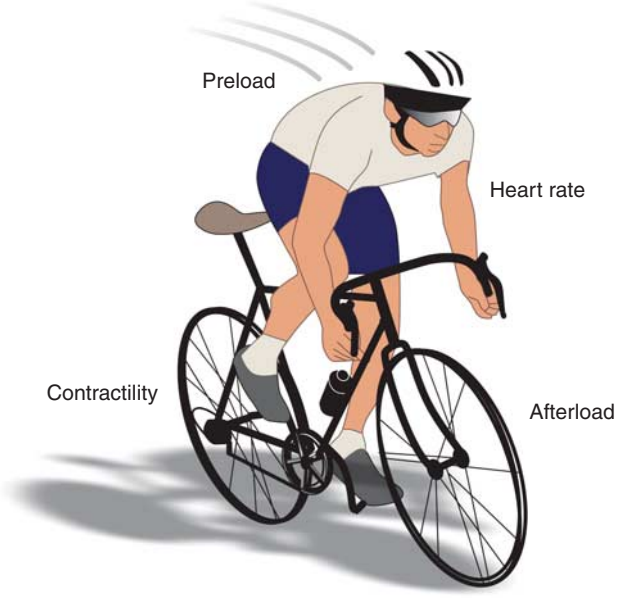

Figure 2 | Representation of the four determinants of cardiac output using as an analogy the speed of a bicycle (adapted from Vincent[1]).

decrease in cardiac output that may alter tissue perfusion. The optimal heart rate for each patient is, however, difficult to determine, as it depends on intrinsic contractility, volume status, adrenergic state, and diastolic function.

Contractility depends on the muscular force of contraction, and its implication is obvious. However, the force of contraction is also a determinant of myocardial oxygen demand, and increasing it may rapidly result in fatigue, as with the cyclist pedaling too hard who eventually has to slow and stop. This same situation can occur with excessive inotropic support, and is associated with increased mortality rates. This observation may explain why the long-term effects of inotropic agents have been disappointing, but β-blocking agents have been more beneficial in the long-term treatment of patients with congestive heart failure. Short-term use of inotropic agents may, however, be appropriately required for treating inadequate cardiac output in the context of impaired tissue perfusion, as the benefits may outweigh the myocardial risks.

Preload is the degree of myocardial distension before shortening, and can simplistically be compared with a tailwind allowing the cyclist to move faster without any additional muscular effort. Preload depends on volume status and on diastolic function and time (and thus on heart rate). Although preload is often already increased in patients with established renal failure who have volume overload secondary to oliguria, these patients also frequently have impaired diastolic function related to myocardial muscle hypertrophy and/or ischemic problems. It is noteworthy that during hemodialysis, preload is often decreased as a consequence of fluid withdrawal, and impaired cardiac function may explain the poor tolerance to fluid withdrawal in some of these patients. In particular, patients with diastolic dysfunction have a poor therapeutic window between pulmonary edema, due to increased hydrostatic pressure in lung capillaries, and low stroke volume because of insufficient preload. In patients with circulatory failure, optimization of preload should

always be considered. Clinically, this is accomplished by fluid administration (see below).

Afterload represents the elements against which the ventricles must work in order to eject blood, and is largely dependent on arterial blood pressure and vascular tone. In our analogy, decreasing afterload is similar to our cyclist moving from a bumpy road to a smooth one or one with a gentle downhill slope, where the bicycle's speed can increase significantly for the same degree of muscular effort. The tired cyclist, or the failing heart, is particularly sensitive to these aspects. The administration of strong vasopressors, such as phenylephrine, may restore blood pressure but may decrease cardiac output by increasing afterload, even in individuals with normal cardiac function. This is observed especially if hypovolemia coexists, which is why it is so important to assess fluid requirements using a fluid challenge technique (see below) in patients being treated with vasopressor agents. Vasopressin may also decrease cardiac output by increasing vascular tone.[2,3] Similarly, vasodilators can increase cardiac output, especially in conditions in which contractility is impaired. This is why norepinephrine is usually preferred as a vasoconstrictor: it is an effective vasoconstrictor because of its α-adrenergic effects, yet it retains some inotropic effects via its moderate β-adrenergic effects. Afterload is increased (the road is now going uphill) but cardiac muscle contraction is also increased (the cyclist pushes harder on the pedals).

Some drugs, such as phosphodiesterase inhibitors (milrinone, enoximone) and levosimendan, exert combined inotropic and vasodilating effects. This is similar to pushing a bit harder on the pedals at the same time as the road starts to go down; more exertion may lead to fatigue, but the downhill slope helps maintain speed. This is why these 'inodilating substances' may increase myocardial oxygen requirements less than other inotropic agents. However, one has to be very cautious when using phosphodiesterase inhibitors in patients with renal failure as their half-life is markedly increased.

CARDIAC FUNCTION IN SEPSIS

In sepsis, the simultaneous presence of tachycardia and reduced vascular tone results in reduced afterload, and cardiac output can therefore be maintained or even increased. Indeed, sepsis is typically associated with a high cardiac output, a situation referred to as hyperkinetic or hyperdynamic (the two terms are equivalent). Fluid therapy is typically necessary to achieve the hyperkinetic state. This state is usually associated with a normal or high mixed venous oxygen saturation reflecting decreased oxygen extraction by the tissues. Myocardial depression can occur simultaneously, because of the release of cytokines and other mediators, some of which are associated with abnormal calcium handling by the cardiac myocytes,[4,5] leading to reduced myocardial contraction. There is evidence that the more severe the sepsis, the more profound the vasodilation and the myocardial depression. This situation is akin to the cyclist being too tired to push on the pedals, but able to keep up speed because of a strong tailwind and a smooth downsloping road. Importantly, the severity of myocardial depression is sometimes hidden by initial hypotension (decreased afterload) and becomes obvious only after restoration of blood pressure with vasoconstrictive agents.

DISTRIBUTION OF BLOOD FLOW

In acute conditions, when oxygen supply is threatened, cardiac output is preferentially redistributed to the brain and the heart. This is seen in low flow states, such as in acute hemorrhage.[6] In these acute conditions, the natural response is to preserve the ability to think how to react and for the heart to continue to pump as much flow as possible. Renal blood flow is decreased as the resultant decrease in urine production will help to preserve blood volume (an effect that has been called 'acute renal success').[7] Feeding is not a priority in the acute conditions, and appetite is simultaneously reduced.

The persistence of decreased perfusion to the gut and the kidneys is, however, an important preoccupation in critically ill patients. It is expected that patients with persistent hypovolemic or cardiogenic shock would have decreased splanchnic and renal perfusion, but does this also occur in patients with septic shock? Several studies have shown that hepato-splanchnic perfusion is indeed altered in patients with septic shock,[8,9] and the severity of these alterations is related to outcome. For renal perfusion, data are more scarce and these provided conflicting results.[10,11]

MICROCIRCULATORY ALTERATIONS

The microcirculation has a key role in fine tuning perfusion at the organ level. Several studies have shown that microvascular perfusion is altered in sepsis[12] or in severe heart failure,[13] even when global circulation is maintained at resuscitation goals. Admittedly, evaluation of the renal microcirculation is still not feasible in humans, but experimental studies suggest that the renal microcirculation is impaired in sepsis.

In addition, the kidney has some peculiarities; for example, perfusion to the cortex, mainly containing glomeruli, differs from that to the medulla, mainly containing tubules. Because of microcirculatory shunting, which already occurs in normal conditions, the PO_2 of the medulla is markedly altered, whereas the PO_2 of the cortex is close to arterial PO_2. Any decrease in renal perfusion will result in a decrease in medullar PO_2, which may reach critical values for the very active tubular cells, leading to tubular necrosis. In sepsis, alterations in renal microvascular perfusion, in conjunction with increased oxygen requirements in the tubules,[14] may contribute to renal failure even when total renal perfusion is preserved.[10]

In fluid-resuscitated endotoxic animals, Johannes *et al.*[15] reported that cortical and medullar PO_2 decreased despite an increase in renal perfusion. More recently, Legrand *et al.*[16] reported in endotoxic rats that sepsis alters renal microvascular perfusion and oxygenation distribution. More

importantly, fluid administration, especially when performed early, improved microvascular blood flow distribution but failed to prevent the alteration in PO_2 distribution. Altogether, these data suggest impaired oxygen balance in the kidneys, despite preservation of renal perfusion, especially after fluid resuscitation.

KIDNEY PERFUSION: PRESSURE VS. FLOW

To ensure adequate oxygen delivery to the tissues, attempts are often first made to optimize perfusion pressure and then to optimize flow, but these two components may be directly related. In normal conditions, organ blood flow remains relatively constant over a wide range of pressures, because autoregulation of blood flow induces vasoconstriction as pressure increases and vasodilation when it decreases. However, organ injury can impair this phenomenon, so that organ blood flow becomes directly proportional to the pressure in the organ.

In dogs, Bellomo *et al.*[17] reported that endotoxin alters renal autoregulation. For a given mean arterial pressure, renal blood flow was lower in sepsis. Interestingly, administration of norepinephrine increased pressure but decreased renal perfusion in normal conditions, whereas it increased pressure and renal perfusion in endotoxic conditions. In addition, kidneys may be sensitive to flow. In an ovine model of septic shock, the addition of levosimendan was associated with an improvement in renal function, even though mean arterial pressure was identical to that of the control group.[18]

Restoring or maintaining a sufficient perfusion pressure should, therefore, be a first goal. There have been a number of clinical reports showing that norepinephrine administration may increase urine output.[19,20] Restoration of urine output may be indicative of the optimal arterial pressure level. But what is this optimal level? In patients with septic shock, Martin *et al.*[20] showed that increasing mean arterial pressure from 54 to 75 mm Hg was associated with improved urine output and creatinine clearance.[21] However, Ledoux *et al.*[22] and Bourgoin *et al.*[23] failed to observe significant changes in urine output and/or creatinine clearance when increasing mean arterial pressure from 65 to 75 and 85 mm Hg. Interestingly, there may be individual variability in the response. When individual response rather than group data were reported, it became obvious that some patients may benefit from a further increase in blood pressure. Using renal Doppler measures as a surrogate for renal blood flow, Deruddre *et al.*[24] observed that renal perfusion increased in some but not all patients when increasing mean arterial pressure from 65 to 75 mm Hg. This improvement in renal Doppler was associated with an increase in urine output.

It is only when renal perfusion pressure has been restored that increasing renal blood flow may be worthwhile. In endotoxic shock, De Backer *et al.*[25] reported that a low dose of dobutamine (5 mcg/kg/min) improved renal perfusion and urine output. In patients with cardiac failure, a low-dose dobutamine infusion also improved urine output. As renal arteries have more dopaminergic receptors than the rest of the body, the use of dopaminergic agents was believed to be a rational approach;[26] unfortunately, a large prospective randomized controlled trial from Australasia did not show any clinically measurable renal protection with low-dose dopamine.[27] More recently, in a large trial in which vasopressor doses of dopamine and norepinephrine were compared in the treatment of shock, dopamine administration did not result in improved renal function; moreover, dopamine administration resulted in more arrhythmias than did norepinephrine administration.[28] In addition, dopamine may decrease the immune response by preventing prolactin release.[29] The use of fenoldopam as a pure dopaminergic agent may be an alternative, but this purely vasodilating substance may decrease arterial pressure, which could limit its use in critically ill patients.

Alternatively, one may consider increasing glomerular filtration by preferential constriction of efferent arterioles. This effect may explain why vasopressin—despite its natural antidiuretic effects—may paradoxically increase urine output and perhaps even creatinine clearance in patients with septic shock.[30] However, as mentioned above, one has to be very cautious in the use of this agent, avoiding excessive increase in arterial pressure, which may have detrimental effects on heart function, and avoiding excessive doses, which can have detrimental effects, including on splanchnic perfusion.

KIDNEY FUNCTION IN SEPSIS

Focusing only on the hemodynamic alterations is not enough. Sepsis is a common cause of acute renal failure in the critically ill,[31] and hemodynamic stabilization in such patients is often not sufficient. In contrast to earlier beliefs that renal blood flow is decreased in sepsis, leading to renal vasoconstriction and ischemia, more recent evidence indicates that renal blood flow is typically increased in animal models and at least normal in humans.[10,11] Although glomerular filtration is markedly reduced in septic acute renal failure, pathologic studies have shown few structural changes; those that are present are primarily restricted to the tubular epithelium. Although endothelial and interstitial changes may also occur, the histopathological alterations are very limited, with hardly any evidence of tubular damage. Hence, although microcirculatory disturbances may contribute to an altered distribution of blood flow within the kidneys, sepsis-related renal failure is rather an immune-mediated phenomenon, associated with cytokine release, increased nitric oxide formation, oxidative stress, mitochondrial damage, and increased apoptosis.[11]

IS SHOCK-RELATED ACUTE RENAL INSUFFICIENCY PROTECTIVE?

As renal metabolism is highly energy demanding, some have hypothesized that the shut down of renal function may be adaptive, improving the balance between oxygen demand and supply in renal cells.[7] Indeed, as renal oxygen consumption is mostly driven by sodium tubular readsorption, reduction in glomerular filtration should lead to a reduction in the renal

reabsorptive workload, and thus renal oxygen consumption. This concept is supported by the fact that acute tubular necrosis is uncommonly observed in patients with septic shock. However, this idea has been challenged recently. In post-cardiac surgery patients, renal oxygen consumption was found to be similar in patients with and without acute renal failure, whereas glomerular filtration, renal blood flow, and sodium readsorption were found to be lower in patients with acute renal failure than in the patients with normal renal function.[14] Accordingly, renal consumption per unit of sodium reabsorbed in patients with renal dysfunction was more than twice that in patients with normal renal function. This suggests that renal dysfunction represents renal failure more than renal success.

A PRACTICAL HEMODYNAMIC APPROACH

Restoration/maintenance of blood volume

The first logical intervention is to restore an adequate blood volume with fluid administration. Decreased urine output is a hallmark of renal hypoperfusion, and restoring urine output is an important target in acute renal failure. A reduction in urine output is actually a more frequent sign of acute renal failure than an increase in creatinine.[32,33] There is no good evidence that diuretics can protect the kidneys, and some evidence that they may have harmful effects.[34] There is also evidence that edema formation, occurring as a result of excess fluid administration, can alter tissue function.[35] This concept is also true in the kidney, where edema can result in higher intracapsular pressures.[36] In a large European study, in which the time course of organ failure was studied, renal failure was often preceded by a period of positive fluid balance.[37] Importantly, Macedo *et al.*[38] reported that fluid accumulation could dilute serum creatinine, thus leading to underestimation of the increase in serum creatinine and delayed diagnosis of renal dysfunction or failure.

It is therefore essential to carefully evaluate the volume status of the patient, so as to avoid both hypo- and hypervolemia. Assessing fluid requirements is, however, not easy. Assessment of heart rate is neither sensitive nor specific. In contrast to the typical pressure response to volume status in chronic renal failure, the arterial pressure tells very little about the fluid status in the critically ill. As arterial pressure is determined by cardiac output and vascular tone, hypotension may result from alterations in any of the determinants of cardiac function discussed above—hypovolemia, myocardial failure, severe arrhythmia, or obstruction (as in massive pulmonary embolism or tamponade)—or from profound alterations in vascular tone, such as those that occur in severe sepsis. Cardiac filling pressures provide very little information regarding the volume status of an individual patient, and can only give a statistical likelihood of a response to fluids, from around 80% when the cardiac filling pressures are low to less than 40% when they are high.[39] The central venous pressure may be elevated even in the presence of relative hypovolemia in patients with pulmonary hypertension, such as patients with chronic lung disease.

Ultimately, the response to fluids is characterized by an increase in stroke volume associated with an increase in cardiac filling, corresponding to a positioning on the ascending limb of the Frank–Starling curve. For the tissues, it is the resulting increase in cardiac output that will increase oxygen transport.

Several techniques can be used to try to predict the response to fluids. In patients under mechanical ventilation, respiratory variations in stroke volume or its derivates (pulse pressure, phlethysmography) are associated with a high likelihood of hemodynamic response to fluids.[40] Unfortunately, these indices are not valid in patients with arrhythmias, spontaneous ventilation, or low tidal volume,[41] and thus these techniques can only be applied in selected patients. In addition, perfect coordination with the respirator requires deep sedation, which we prefer to avoid today.[42] Indeed, all sedative agents alter vascular tone and may also decrease myocardial contractility, thus altering the hemodynamic status. The use of prolonged sedation also prolongs the recovery phase and rehabilitation.

The passive leg raising test may also be used to predict fluid responsiveness,[43] but for this test patients must be able to tolerate a rapid change in torso position (this may not be the case in some surgical patients and in patients with cerebral edema) and it requires the use of rapid response cardiac output monitoring. Here, also, sedation may be required to prevent stress-related sympathetic stimulation, which may increase heart rate and cardiac output in all individuals, regardless of their volume status.

In addition to the intrinsic limitations of these tests, one should recognize that the results of these tests are not dichotomic (i.e., no response below a given value, response above that value); there is rather a continuum, with the likelihood of response to fluids increasing when the value increases, so that there remains a 'gray zone' in which there is still some incertitude. Hence, these tests do not negate the need for a fluid challenge.[44] Rather, when physicians use these tests to predict fluid responsiveness, it is still wise to use a fluid challenge technique when administering the fluids in order to ensure that the response to fluid is indeed positive and that they are tolerated.

Ultimately, trial and error is the best approach. As an example, what would we do if urine output increased by 40 ml after administering 1 liter of intravenous fluids? Would we continue infusion with the risk of creating a similar positive fluid balance, i.e., almost one liter of fluid accumulating in the body, or would we stop (and risk losing the benefits?). The answer lies in the cardiac filling (pressures or volumes). Because volumes represent ventricular preload better than pressures, one may consider that measurements of volume are of greater value. However, as edema formation is dependent on intravascular pressures, it may be better to base our decisions on filling pressures rather than volumes. In addition, the relationship between pressures and volumes is curvilinear so that pressures increase rapidly when a given volume is exceeded.[45] This is why the fluid challenge

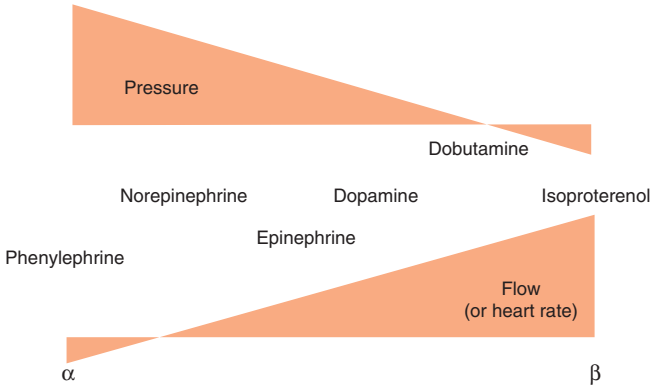

Figure 3 | Principal adrenergic agents presented according to their relative β- (primarily increasing flow) and α- (primarily increasing pressure) effects.

technique was developed,[44] enabling the patient's response to fluids to be determined while minimizing the risks of edema (pulmonary edema in particular).

When performing a fluid challenge, four items must be defined in advance, which can be summarized by the acronym, TROL:

1—**T**ype of fluid (e.g., Ringer's lactate)

2—**R**ate of infusion (e.g., 500 ml in 30 min)

3—**O**bjective (e.g., increase in arterial pressure to 75 mm Hg or urine output greater than 20 ml in 30 min);

4—**L**imits (e.g., a maximal increase in central venous pressure of 3 mm Hg from a baseline of 12 mm Hg).

If the target improves but is not reached with the fluid challenge, and the safety limits are not breached, fluid challenges can be repeated until such time as there is no further improvement in the objective or the safety boundaries are exceeded. Repeated fluid challenges can thus be given as long as the response suggests continuing hypovolemia, thus limiting the risks associated with fluid overload.

Restoration/maintenance of perfusion pressure

When blood volume has been restored and fluid therapy is no longer beneficial, vasoactive agents are needed to restore/maintain perfusion pressure. In the hypotensive patient, vasopressors should be used as the first-line strategy. The choice of vasopressor agent has already been discussed above and Figure 3 presents the effects of currently used vasoactive agents on arterial pressure and cardiac output.

CONCLUSION

Cardiovascular alterations in the critically ill are complex and not limited to low flow states. Sepsis, in particular, is a frequent cause of renal failure in which renal blood flow is typically preserved. In all cases, optimization of blood volume and tissue perfusion pressure is of paramount importance. A number of variables need to be combined to build a complete picture, which will then enable appropriate treatment choices to be made based on a sound physiological approach.

DISCLOSURE

All the authors declared no competing interests.

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